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## Proctitis: a glance beyond inflammatory bowel diseases

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**PROCTITIS:  
A GLANCE BEYOND INFLAMMATORY BOWEL DISEASES**

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## Abstract

Proctitis is an inflammation involving the anus and the distal part of the rectum, frequently diagnosed in the context of inflammatory bowel diseases (IBD). Nevertheless, when the standard therapy for IBD is ineffective, it becomes necessary for the clinician to review alternative etiologies, beginning from the broad chapter of infectious causes up to rare causes such as radiation, ischemia, diversion and traumatisms. While it is possible to find infectious proctitides caused by pathogens generally inducing extensive colitis, the growing incidence of both sexually transmitted infections and isolated proctitis reported in the recent years require a lot of attention. The risk appears to be higher in individuals participating in anal intercourse, especially men having sex with men (MSM) or subjects who use sex toys and participate to sex parties, dark rooms and so on. The commonest implicated pathogens are *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, Herpes Simplex virus and *Treponema pallidum*. Herpes and Chlamydia infections mainly occur in HIV-positive MSM patients. Since symptoms and signs are common independently from etiology, performing a differential diagnosis based on clinical manifestations is complicated. Therefore, the diagnosis is supported by the combination of clinical history and physical examination and, secondly, by endoscopic, serologic and microbiologic findings. Particular emphasis should be given to simultaneous infections by multiple organisms. The involvement of experts in infectious diseases and in sexual health is crucial for the diagnostic and therapeutic management. The available therapies, empirically initiated or specific, in many cases are able to guarantee a good prognosis and to prevent relapses.

Proctitis is an inflammation confined to the distal 12-15 cm of the rectum. The most common type is part of chronic inflammatory bowel diseases (IBD), conditions of unknown etiology including Crohn's disease and ulcerative colitis<sup>1</sup> and presenting with rectal bleeding, diarrhea, tenesmus, discharge, cramps and pain on the left side of the abdomen during the bowel movement. Proctitis as part of IBD has a good response to topical and oral therapy with 5-aminosalicylic acid (5-ASA) and/or prednisone, but it may also have a more aggressive course, especially in the context of Crohn's disease of the ano-rectal region, so that a therapy with biological drugs or immune-modulators could be required.<sup>2,3</sup>

Despite these well-known aspects of IBD, it is necessary to emphasize how proctitis could be ascribed to other causes, infectious and not. It is not rare, for clinicians, to deal with clinical cases having an initial diagnose of IBD but over time not responder to standard therapy and, therefore, requiring a good attitude to take into consideration other etiologies.

Considering infectious etiologies, this review highlights on the main pathogens acting in the rectum as a prevalent or exclusive site. Among non-infectious causes, those due to radiation ischemic, diversion and traumatic proctitis will be discussed.

**Table 1. Etiology of proctitis.**

INFECTIOUS	NON INFECTIOUS
<p><b>1. Sexually transmitted pathogens (isolated proctitis)</b></p> <ul style="list-style-type: none"> <li>• <i>Neisseria gonorrhoeae</i></li> <li>• <i>Chlamydia trachomatis</i></li> <li>• Herpes Simplex virus</li> <li>• <i>Treponema pallidum</i></li> <li>• <i>Haemophilus ducreyi</i></li> <li>• Cytomegalovirus</li> </ul> <p><b>2. Sexually and non sexually transmitted pathogens (extended colitis)</b></p> <ul style="list-style-type: none"> <li>• <i>Campylobacter jejuni</i>, <i>Shigella</i>, <i>Entamoeba histolytica</i>, <i>Giardia lamblia</i> and others.</li> </ul>	<ul style="list-style-type: none"> <li>• Inflammatory bowel diseases</li> <li>• Radiation therapy</li> <li>• Ischaemia</li> <li>• Surgical diversion</li> <li>• Trauma (anal intercourse, fisting, masturbation)</li> </ul>

**Clinical and endoscopic findings in patients with proctitis**

Regardless of the specific etiology, the clinical pictures and endoscopic characteristics are often superimposable in patients with proctitis, so further investigation are needed to trace the exact cause, as it will be explained below. Peculiar symptoms include: diarrhea (mild or severe), urgency, tenesmus, cramping pain during bowel movements, mild/severe rectal bleeding, hematochezia, involuntary spasms, pruritus, anorectal discharge (pus), anal warts and the feeling of incomplete emptying of the bowel. Endoscopic findings associated with acute injury include edema, erythema, friability and mucosal ulceration, while, in the chronic cases, distinctive findings are nodules, inflammatory polyps, abscesses, fistulae and strictures

**Table 2. Common clinical manifestations and endoscopic features in patients with proctitis.**

Clinical manifestations	Endoscopic features
Diarrhea	<b>Acute injuries:</b>
Stool urgency	Edema
Tenesmus	Erythema
Cramping pain	Friability
Rectal bleeding	Ulceration
Hematochezia	<b>Chronic injuries:</b>
Involuntary spasms	Nodules
Anorectal discharge	Abscesses
Pruritus	Fistulae
Anal warts	Strictures
Feeling of incomplete emptying	Inflammatory polyps

## INFECTIOUS PROCTITIS

### Sexually transmitted pathogens

In several cases it is essential to take into consideration pathogens which are specifically responsible of isolated proctitis. In the last years, indeed, there has been a rising incidence, especially in men have sex with men (MSM), of sexually transmitted infections (STIs), which can have proctitis as the main manifestation. This often occurs in healthy patients presenting with rectal symptoms, so that gastroenterologists or other specialists dedicated to proctology are required to have an adequate knowledge of the potential etiological agents in order to guide the proper approach and a successful therapeutic intervention.

It is unavoidable to collect a detailed and careful clinical history regarding recent traveling history and also risk behaviors, such as anal intercourse and number of sexual partners. The most frequent agents of infectious proctitides are represented by *Neysseria gonorrhoeae* (*N. gonorrhoeae*), *Chlamydia trachomatis* (*C. trachomatis*), Herpes Simplex virus (HSV) and *Treponema pallidum* (*T. pallidum*). In about a half of cases the infectious cause is not identifiable.<sup>4</sup> Furthermore, should be considered the possibility to find coinfections with two or more pathogens (10% of all cases). Once an infectious proctitis is diagnosed, all STI sample testing, including human immunodeficiency virus

(HIV), are mandatory. In case of suspicious of a STI, patients must be submitted to a STI Clinic to assess all possible sexually transmitted co-infections.

### ***Neysseria Gonorrhoeae***

*N. gonorrhoeae* represents the most frequent bacterial cause of infectious proctitis and the second most prevalent STIs in the United States; however, the actual number of cases is likely much higher due to asymptomatic infections or self administered therapy.<sup>5,6</sup> *N. gonorrhoeae* is a Gram-negative bacterium, facultative intracellular, obligate aerobe and able to move with twitching motility. It typically appears in pairs, diplococci, and resembles the shape of coffee beans. The way of transmission is by direct contact of mucosal surfaces, and so gonorrhea is commonest in individuals participating in receptive anal intercourse, typically in MSM,<sup>7-9</sup> while in females it can be transmitted to the anal canal via a genital infection due to the proximity of the vagina, even in the absence of receptive anal intercourse.

The most typical symptoms, not allowing alone to achieve a differential diagnosis from other infectious causing proctitis, occur after 5-7 days of incubation and include tenesmus, rectal bleeding, pruritus, lower abdominal pain, diarrhea and anorectal purulent discharge. In a small part of cases this infection can be asymptomatic.<sup>10</sup>

Due to the lack of sensitivity and specificity of the clinical diagnosis it is necessary to proceed to a microbiological diagnosis. The test of choice is NAAT (Nucleic Acid Amplification Testing, eg. polymerase chain reaction or PCR) which is the most sensitive. If this method is unavailable it is possible to evaluate the presence of Gram-negative diplococci in Gram stain of mucosal biopsies or purulent discharge, with a sensitivity of 90–95%,<sup>11</sup> or with culture executed on Thayer-Martin agar, which prevents the overgrowth of other endogenous flora. Appropriate material for culture should be obtained using a swab through the anal canal into the distal rectum or under direct vision via proctoscopy.<sup>10</sup> Culture has the advantage to assess antibiotic susceptibilities but the results are not usually available until 48 hours: its sensitivity is 72-95%, declining in asymptomatic patients to 65-85%.<sup>12</sup> When no specific diagnostic test is available, the diagnosis of gonorrhea remains presumptive.

Rectal gonorrhea should be treated with ceftriaxone 250 mg intramuscularly (i.m.) in a single dose, alongside oral azithromycin 1 g once. Alternatives oral antibiotics can be cefixime 400 mg once daily or doxycycline 100 mg once daily for 7-10 days.<sup>13</sup> Gonorrhea is becoming increasingly resistant to cephalosporins and so it is better to verify eradication by repeating testing at the end of treatment in order to prevent further resistance development. Co-treatment with azithromycin and ceftriaxone may



improve eradication of the bacterium and allows to slow down the development of further cephalosporin resistance. Differential diagnosis must be performed with other STI but also with criptitis and anal abscess.

**Fig. 1. Anal cryptitis caused by *N. gonorrhoeae*.**

### ***Chlamydia trachomatis***

*C. trachomatis* belongs to a group of obligate intracellular parasites of eukaryotic cells which can replicate only within a host cell. It has a life cycle consisting of two morphologically distinct forms: firstly *C. trachomatis* attaches to a new host cell as a small spore-like form, called elementary body, which penetrates the host cell, surrounded by a host vacuole, called inclusion. Within the inclusion, *C. trachomatis* turns into a bigger and more metabolically active form called reticulate body.<sup>14</sup>

*C. trachomatis* serotypes L1, L2 and L3 are the responsible pathogens for “linfogranuloma venereum (LGV)” and especially serotype L2 has been reported to be mostly implicated,<sup>15,16</sup> while serovars A–K are responsible for the non-LGV infections.

#### **1. Linfogranuloma Venereum**

LGV, also known as “Durand–Nicolas–Favre disease” and “lymphogranuloma inguinale” is an uncommon sexually transmitted disease (STD). The ways of transmission are vaginal, oral or anal sex. In the last 20 years the incidence of LGV has shown a remarkable increase in Europe and North America but it still remains more common in the tropical and subtropical regions around the world.<sup>17</sup> The highest incidence of LGV occurs in the sexually active population between 15 and 40 years. LGV probably affects both sexes equally, although it is more commonly reported in MSM,<sup>18</sup> in whom emerges as a leading cause of proctitis and proctocolitis.<sup>19</sup> It is important to emphasize that LGV patients are frequently HIV-positive MSM with proctitis (85%) and approximately 50% carry other STIs.<sup>20</sup>

LGV has different stages of infection: a primary stage characterized by the appearance of painless genital ulcer or papules at the site of inoculation, which, if unnoticed, can evolve in a secondary stage,

with the development of unilateral or bilateral tender inguinal and/or femoral lymphadenopathy (also called “buboes”). In the secondary stage, symptoms of infection are local, such as tenesmus, anal pain, mucous and bloody rectal discharge, but also systemic like body aches, headache, and fever. In a quarter of the cases patients manifest only rectal symptoms without the development of a lymphadenopathy.<sup>21</sup>

Longstanding LGV can lead to a late stage of the disease with the development of fibrosis, strictures and fistulae of the ano-genital area, findings which can mimic histological, endoscopic and radiological views of IBD or anal cancer.<sup>22</sup>

Currently, a definitive diagnosis of LGV is based on serological tests as complement fixation titers > 1:64 or micro-immunofluorescence titers > 1:256.<sup>19, 23</sup> However, the interpretation of these tests have not been yet standardized or validated for rectal infections so that, in most circumstances, the diagnosis of LGV is based on epidemiological and clinical findings with the supports of methods of identification of *C. trachomatis* in genital, rectal and lymph node specimens like culture (although it is difficult and requires a special medium, cycloheximide-treated McCoy or HeLa cells, and yields are still only 30-50%), NAAT or direct immunofluorescence of rectal swabs or lymph node aspirate.<sup>17</sup> Since this has implications for the duration of treatment, genotyping might be required as an additional test to distinguish LGV from non-LGV. HIV testing should be a consideration in patients with a STD.

Treatment, based on the clinical experience of more than 50 years, considers, as first line, a course of doxycycline 100 mg twice daily for 3 weeks.<sup>13, 24-26</sup> This duration is mandatory because these infections are more invasive and harder to eradicate than uncomplicated genito-urinary tract infections, which generally require only 1 week of treatment. A valid alternative is represented by oral erythromycin 500 mg four times daily for 3 weeks, although its use can be limited by gastrointestinal intolerance. This option is recommended for pregnant women,<sup>27</sup> while doxycycline and other tetracyclines should be avoided in pregnancy due to the risk of disruption of bone and teeth development. Despite the lack of clinical evidence supporting the routine use of azithromycin, it could also be effective as additional option for treating LGV, given its efficacy against other genital tract and systemic non-LGV *Chlamydia* infections. Fluoroquinolone antibiotics with demonstrated anti-*Chlamydia* activity, such as levofloxacin, ofloxacin, moxifloxacin, may also be useful for treating LGV, but no comparative treatment trial has been published. Treatment of asymptomatic rectal *Chlamydia* infections is still controversial.<sup>28</sup> Asymptomatic sexual partners should also be treated with a course of doxycycline, 100 mg twice daily for 1 week.

**Fig. 2. Linfoagranuloma Venereum.****1. Non-LGV Chlamydial proctitis**

*C. trachomatis* serovars A–K are responsible for the non-LGV infections. Transmission is similar to that of *N. gonorrhoeae* and the infection may occur after anal receptive intercourse. Symptoms usually appear 7–10 days after infection and, in over 50% of cases registered in MSM, they are limited to the anal area, without urethral infection. They consist of anal pain, diarrhea, tenesmus, blood and mucous discharge and, sometimes, generalized symptoms as fever. The infection can also be asymptomatic in up to 50-70 % of patients.<sup>29</sup>

Sigmoidoscopy can show findings difficult to distinguish from IBD: friability and erythema of the mucosa with ulcerations and a “cobblestone” appearance for the infiltration of underlying lymphoid follicles. Histological examination can reveal granulomas, another non-specific finding generating confusion with IBD.

Microbiological diagnosis is based on culture or NAAT on rectal swabs. NAAT has been estimated to have a sensitivity of about 90% and a specificity of about 99% in cervical swab and by urine specimen<sup>30</sup> but recent evidences indicates that it may give reliable results on rectal specimens. Moreover, it could be useful to analyze with Aptima combo 2 (Hologic Gen-Probe) that is a transcription mediated assay with the advantage of detecting both *N. gonorrhoeae* and *C. trachomatis*.<sup>31</sup>

Treatment of proctitis takes into consideration doxycycline 100 mg twice daily for 1 week. Alternatively, with comparable efficacy, it is possible to use azithromycin 1 g as a single dose<sup>32</sup> although up to 20% of failure has been observed and therefore it is recommended to repeat NAAT after 6 weeks from the end of treatment. It is advisable to start the same therapy in sexual partners and to consider the high risk of a co-infection with *N. gonorrhoeae* and, therefore, starting empiric treatment against the latter in patients with non-LGV *C. trachomatis* infection.

**Herpes simplex virus**

Herpes simplex virus (HSV) is one of the most known and widespread infections in humans, involving about 60-95% of the adult population worldwide, more than 400 million persons.<sup>33,34</sup> It is the most common viral coinfection among HIV positive patients, with up to 95% of MSM.

HSV infection has been involved in several diseases.<sup>35,36</sup> Therefore, its constant epidemiologic monitoring is considered of high relevance for public health in order to decrease the risk of neonatal HSV infection and associated diseases.<sup>37</sup> Seroprevalence for HSV-1 is present in 93% of the adult population but seroprevalence of HSV-2 is lower, confined to 5.5% in adults<sup>38</sup> and frequently associated with other STDs. In US, according to the US Centers for Disease Control and Prevention, it has been reported a seroprevalence, in the years 2005-2008, of 16.2%.<sup>16</sup>

The two types of HSV, HSV-1 and HSV-2, are both DNA viruses transmitted by direct contact with infected secretions. HSV-1 is generally associated to infections manifesting around labial, oral, and ocular areas, while HSV-2 is associated to lesions around ano-genital area. However, it is frequent to have overlap infections and recent studies demonstrated an increase in ano-genital manifestations due to HSV-1, primarily in developed countries and probably secondary to a greater diffusion of oro-genital sex practices, especially in MSM.<sup>39,40</sup> HSV is second only to *N. gonorrhoeae* as a sexually transmitted cause of infectious proctitis in MSM.<sup>41,42</sup> Moreover, in a recent review, it was postulated a leading role for HSV in causing proctitis in HIV-infected patients.<sup>43</sup>

Once the virus has entered the host, HSV creates a persistent and latent infection: in fact, it remains in a dormant state inside the neuronal ganglia, near the spinal cord, and periodically reactivates, travelling through the nerve fibers back to the skin, causing symptoms again. Recurrence has been reported to occur in about 60% of those infected with HSV-1 and in 90% of those with HSV-2.<sup>11</sup>

HSV-2 is transmitted by anal receptive intercourse and risk factors for contracting infection include: greater lifetime number of sexual partners, female sex, older age, poverty, cocaine use.<sup>44</sup> Primary HSV infection may be asymptomatic, but 40% of men and 70% of women will develop systemic features including general malaise, headaches and muscle pains. HSV-associated proctitis appears 7-21 days after exposure and includes the following symptoms: tenesmus, anorectal pain, rectal bleeding, perianal ulcerations, diarrhea or constipation, inguinal lymphadenopathy and the presence of diffuse ulcerative or discrete vesicular or pustular lesions in the distal 5 cm of the rectum. Most individuals with HSV proctitis present neurologic involvement, in the distribution of sacral roots. This induces difficulty in initiating micturition, paresthesia of the buttock or perineal region or impotence, as reported in more than a half of the patients affected.<sup>45</sup> Subsequently, the lesions evolve in crusts which are followed by healing after 2 weeks. After the start of antibody production to HSV-2, the virus becomes latent and can be reactivated leading to a recurrence of proctitis. In the latter case, proctitis has a course that is milder in symptomatology and decrease in frequency over time.<sup>13,16</sup>

Characteristic findings in sigmoidoscopy consist of mucopurulent exudates, friable mucosa, vesicles and ulcerations. If external lesions are absent the suspicion of HSV infection should persist

because these findings are reported in only about 30% of the patients affected at the time of the diagnosis.<sup>40</sup>

Currently, PCR assays for HSV-DNA, viral cultures and direct fluorescent antibody (DFA) are commonly used for the diagnosis, with immunohistochemistry demonstrating to be one of the best tool among them. In fact, DFA is highly sensitive and specific and permits to distinguish between numerous viruses using specific monoclonal antibodies.<sup>44</sup> In alternative, it is possible to use serology, with assays based on the HSV-specific glycoprotein G1 (HSV-1) and glycoprotein G2 (HSV-2) and can reliably distinguish HSV-1 from HSV-2.<sup>46</sup> An historical test is the Tzanck smear of samples obtained by scraping of an ulcer base: it would permit diagnosis revealing multinucleated giant cells or intranuclear inclusion bodies. However, this test has a limited sensitivity and specificity and has been largely replaced by DFA. Treatment for the first clinical episode is based on a cycle of 7–10 days with one of the following oral antiviral therapies: acyclovir 400 mg 3 times daily, acyclovir 200 mg 5 times daily, valacyclovir 500 mg twice daily, famciclovir 250 mg 3 times daily.<sup>47</sup> Pain control with local anesthetics and warm soaks could be useful as a supportive care. In immunosuppressed individuals or in case of frequent/severe recurrences it should be considered a long-term daily suppressive antiviral therapy to reduce the risk of further episodes of HSV proctitis.

### ***Treponema pallidum***

Belonging to the spirochete group, *T. pallidum* is a pathogen causing an infectious disease called “syphilis”. Approximately 17.7 million individuals, 15–49 years of age, globally have contracted syphilis in 2012, with an estimated 5.6 million new cases every year.<sup>48,49</sup> The estimated prevalence and incidence of syphilis varies by country, with the highest prevalence in Africa. In general, the incidence of syphilis both in men and women has risen in recent years, especially in MSM, and syphilis remains a continuing public health challenge globally.<sup>50</sup>

*T. pallidum* is an obligate human pathogen very invasive and immunoevasive,<sup>51,52</sup> able to induce local inflammatory response by replicating within the tissue and so causing clinical manifestations. Transmission occurs during sexual contact with an actively infected partner and it has been reported that exudate containing as few as 10 organisms can transmit the infection and induce the disease.<sup>53</sup>

The typical course of the disease is divided into primary, secondary, latent and tertiary stage over a period of  $\geq 10$  years. Primary syphilis presents on average within 3 weeks of exposure (or better within 30–90 days), with a painless solitary ulcer (chancre), indurated and with discharge serous fluid, and a regional lymphadenopathy that may involve genitalia, rectum or mouth. Symptoms like bleeding,



significant pain and itching can occur.<sup>16</sup> A painless anal fissure is typical of anal infection. This could develop a proctitis. If unidentified, primary disease can evolve to secondary syphilis in 4–10 weeks (but up to 2 years) later, in which bacteremia leads to multisystem disease that may include a lot of clinical manifestations: maculopapular or pustular rash, peripheral neuropathy, hepatitis, periostitis, glomerulonephritis, meningitis, anterior uveitis and interstitial keratitis. The typical rash may form flat, broad, whitish, wart-like lesions on mucous membranes, covered in a greyish exudate, known as condylomata lata, papules commonly perianal or genital in anatomical origin. Condylomata lata are highly infectious. Tertiary syphilis may occur approximately 3–15 years after the initial infection, in one third of people who did not receive treatment, and may be distinguished into three different forms: gummatous syphilis (gummae are granulomatous nodules or ulcers of the gastrointestinal tract or buttocks), late neurosyphilis (dementia, paresis, seizures), and cardiovascular syphilis (aortitis or aneurisms).<sup>54</sup> Up to 2 years after acquisition, early infection without any manifestations of the first two stages is defined as “early latent syphilis”. Primary, secondary and early latent stages of syphilis are infectious, whereas the later stages of tertiary syphilis are largely non-infectious. Therefore, the biggest efforts should focus on diagnosing and treating primary, secondary and early latent syphilis so as to avoid later complications.

A diagnosis of syphilis cannot be made by culture but by using dark ground microscopy and PCR of affected tissues as ulcer exudate, condylomata lata exudate or rectal biopsies. Blood tests are divided into non-treponemal and treponemal tests.<sup>55</sup> Non-treponemal serologic tests are most commonly used to establish a diagnosis: venereal disease research laboratory (VDRL) and rapid plasma reagin (RPR) tests are used to diagnose an initial infection and to monitor response to therapy. False positives on the non-treponemal tests can occur with some viral infections, such as varicella and measles, but also with lymphoma, tuberculosis, malaria, pregnancy and some other conditions. Therefore, treponemal tests, such as treponemal pallidum particle agglutination (TPHA) or fluorescent treponemal antibody absorption (FTA-Abs) test, should be performed because are confirmatory and are required to identify false-positive VDRL or RPR tests. Antibodies may be undetectable within serum before 12 weeks from infection and so repeat blood sample 3 months after the last sexual risk may be necessary. As 40–60% of contactable sexual partners may be infected, contact tracing and screening are required.

Treatment of primary and secondary syphilis consists, as first line, of a single i.m. penicillin G benzathine 2.4 million units. This is a form of penicillin slowly hydrolysed to benzylpenicillin and it permits to improve bioavailability and better monitor. Alternatively, i.m. procaine penicillin 600.000 units daily for 10–14 days can be given. In case of penicillin allergy, an alternative therapy is a 2-week regimen with doxycycline 100 mg twice daily. Recurrent syphilis infections are not rare and the

risk to develop it is substantially increased in case of HIV co-infection: 6.7% of MSM with an initial diagnosis of rectal syphilis experienced a recurrence within one year.<sup>56</sup>

**Fig. 3. Anal fissure and condilomata in syphilis.**

**Fig. 4. Syphilitic proctitis.**

### ***Haemophilus ducreyi***

*Haemophilus ducreyi* (*H. ducreyi*) is a Gram-negative bacterium known as the causative agent of an ulcerating sexually transmitted disease called “chancroid”. Although this infection is rare and its incidence seems to be in decline, the true incidence of chancroid remains uncertain and underdiagnosed because few laboratories are able to correctly approach a microbiologic diagnosis.<sup>57</sup> *H. ducreyi* is transmitted by sexual contact through breaks in the skin during intercourse. Hours to days after exposure, infection manifests as tender papules with erythema that eventually goes into a pustule then an ulceration. The ulcers are typically painful and frequently multiple, but these features are not helpful to distinguish them from ulcers caused by other STDs. The most common site is the genitals, but perianal and anorectal region can be involved with abscesses and ulceration. In 50% of chancroid infections in men it is reported a painful unilateral inguinal adenopathy, which is rare in women.<sup>58</sup>

Diagnosis is based on culture on selective medium but PCR testing is more sensitive than culture for detecting *H. ducreyi*, although it is not widely available. Gram’s stain of material from the base of suspicious ulcers shows Gram-negative rods in small groups, with a sensitivity of 40-60%.<sup>58,59</sup> Treatment is with one of the following alternatives: oral azithromycin 1 g in single dose, ceftriaxone 250 mg, i.m., in single dose,<sup>50</sup> oral ciprofloxacin 100 mg twice daily for 3 days or oral erythromycin base 500 mg twice daily for 3 days.

### **Cytomegalovirus**

Although most of the current guidelines on diagnosis and treatment of STIs do not consider extensively this etiology and although it is mostly considered in the context of proctocolitis, in HIV-immunocompromised patients, some cases of Cytomegalovirus (CMV) isolated proctitis have been reported. CMV infection in MSM is characterized by prolonged excretion of CMV in semen, and is

associated with unprotected anal intercourse: the triad of mononucleosis like illness with rectal bleeding shortly after unprotected anal intercourse are considered as pathognomonic characteristics for sexually transmitted CMV proctitis. Peculiar findings on sigmoidoscopy are rectal mucositis and ulceration. CMV serology and biopsy (including CMV histochemistry) confirm the diagnosis. Suggestive histopathological findings include: enlarged cells with intracytoplasmic and intranuclear inclusion bodies.<sup>61</sup> The role of antiviral therapy in primary CMV proctitis has not yet been defined as very often it spontaneously regresses. However, in patients at risk such as HIV-infected or immunocompromised, the therapy is necessary and is based on the use of ganciclovir and valganciclovir. CMV should be considered in any case of unexplained proctitis.

### Sexually and non-sexually transmitted pathogens

#### *Campylobacter jejuni*

Considered as one of the most common causes of human gastroenteritis in the world, *Campylobacter jejuni* is a Gram-negative bacterium, appearing as curved or comma-shaped rods, able to move via flagella and typically surviving in environments with a low amount of oxygen. Food poisoning caused by its infection can be severely debilitating. In 2017, it has been described an increased incidence of culture-confirmed *Campylobacter* infections, till to 19.2 per 100,000 persons, the highest of all pathogens studied.<sup>62</sup> Although in healthy patients the ingestion of contaminated food (raw or under-cooked poultry, raw dairy products) or water is the main way of transmission, some alternatives could exist. In fact, sexual transmission by practices promoting fecal-oral contact has been reported: *Campylobacter species* have been isolated from stool and rectal cultures obtained from homosexual individuals presenting with proctocolitis.<sup>58,62</sup> The infection is characterized by an inflammatory, sometimes bloody diarrhea or dysentery, associated to cramps, fever, myalgias, chills and abdominal pain, which appear 1-3 days after the infection.<sup>63</sup> The clinical manifestations can be confused with appendicitis or IBD. In HIV-positive patients it is frequent to observe a more severe course with bacteremia, due to its capability to spread in the blood, or with extraintestinal manifestations such as cellulitis and pneumonia.<sup>64</sup>

Usually, endoscopy offers non-specific findings of proctocolitis and is not useful for differential diagnosis. Stool culture is the most reliable tool for the diagnosis.

Treatment is necessary, especially in immunocompromised patients, and is based on azithromycin 500 mg daily for 3 days or erythromycin 500 mg four times a day for 7 days. In immunocompetent



individuals, the infection is self-limiting and, in most cases, symptomatic treatment by liquid and electrolyte replacement is sufficient.

### ***Shigella***

In the genus *Shigella* are included Gram-negative pathogenic enterobacteria known to be the cause of bacillary dysentery (shigellosis). Shigellosis is due to the capacity to invade and colonize the colonic mucosa, particularly the rectosigmoid portion of the colon, leading to its disruption. The most frequent species are *Shigella Flexneri* (*S. Flexneri*) e *Shigella Sonnei* (*S. sonnei*). The transmission of *Shigella* can occur via contaminated food and water and via direct person-to-person spread, but in 1974 its sexual transmission was first reported.<sup>65</sup> Patients with shigellosis typically present with high fever, abdominal cramps, vomiting and bloody, mucoid or watery diarrhea. *S. sonnei* is usually associated to a mild course, in general watery diarrhea, *S. flexneri* commonly causes bloody diarrhea.<sup>66</sup>

Sigmoidoscopy shows a proctitis but inflammation may be extended proximally to the rectum. Diagnosis relies on the presence of erythrocytes, polymorphonuclear neutrophils (PMNs), and mucus in patient stools, which are considered as diagnostic elements. Nowadays, in most laboratories, automated PCR on stool is a commonly used test. In an immunocompetent host, the course of disease is generally self-limited, lasting no more than one week when left untreated.

Treatment consists of supportive care and symptomatic drugs (antimotility agents are contraindicated). Antibiotics can be used in immunocompromised patients and should be selected on the basis of regional antibiotic susceptibility profiles due to the high rate of antibiotic resistance.

### ***Entamoeba histolytica***

*Entamoeba histolytica* (*E. histolytica*) is a protozoan that causes non-febrile intestinal infection, called amebiasis. Although it can occur worldwide, the prevalence is disproportionately higher in low and middle-income countries because of poor socioeconomic conditions and sanitation levels, while in developed countries, amebiasis is generally seen in migrants or travelers coming from endemic areas (Mexico, Latin America and Asia) after a long stay (it is not a common cause of travelers' diarrhea). With over 100.000 deaths per year, it is the third most deadly parasitic infection.<sup>67</sup> The most known way of transmission is the fecal-oral route but it can also be transmitted sexually, both in homosexual and heterosexual individuals.<sup>68</sup> Risk factors for contracting this infection have been mostly identified in MSM, in case of HIV coinfection or oro-anal sexual practices.<sup>69</sup> In 90% of cases,

*E. histolytica* infection is asymptomatic, but there are several factors which may determine the outcome such as genetic susceptibility, young age, corticosteroid or immunosuppressive treatments, malnutrition, malignancy and alcoholism.<sup>70</sup> Amebiasis generally presents a subacute onset, symptoms appear after 1-3 weeks from ingestion of cysts, when trophozoites damage the mucosa causing an inflammatory infiltrate and proctocolitis. Diarrhea can range from mild to severe, with bloody stool, abdominal pain and weight loss, configuring a dysentery syndrome. In some case the course can be deleterious with a fulminant amebic colitis: bowel necrosis leads to perforation and peritonitis, conditions associated to a mortality rate higher than 40%.<sup>71</sup>

Diagnosis is well established by the combination of antigen testing (using monoclonal antibodies to bind specific epitopes in stool and serum) or serology together with identification of trophozoites or cysts on microscopic examination of stool specimens. Antibodies are detectable within 5-7 days of acute infection and may be result positive for years. Also molecular methods may be helpful and PCR techniques can detect *E. histolytica* in stool specimens. Endoscopy shows ulcers, erosions, exudates, edematous cecal mucosa or the common findings which are “flask-like” ulcerations or erosions typically present in the cecum, followed by the rectum and the other segments of the colon.<sup>72</sup> However, in the acute phase, colonoscopy should be avoided because of the risk of perforation due to the instillation of air necessary to expand and visualize the colon.

Treatment is based on nitroimidazole drugs as metronidazole 500 to 750 mg by mouth three times daily for 7-10 days or tinidazole 2 g once a day for 3-5 days.<sup>73</sup> After a 10-day course of a nitroimidazole, paromycin (or, in second line, diiodohydroxyquin and diloxanide furoate) should be administered to assure that the luminal parasites are deleted and to prevent relapse.<sup>74</sup> Promising results are coming from the investigation of vaccines in rodent and non-human primate models.

### ***Giardia Lamblia***

*Giardia Lamblia* (*G. Lamblia*) is a flagellated protozoan parasite, etiological agent of giardiasis. More than 200 million cases of giardiasis are annually diagnosed worldwide, with a higher prevalence in developing countries. This parasite is transmitted via fecal-oral route (water is a major source of transmission) through direct or indirect ingestion of infectious cysts but, sexual transmission has been reported in MSM.<sup>75</sup> Parasites penetrates the human organism adhering and replicating on the brush border of the duodenum and jejunum and feeding on the mucous secretions of the intestine. Clinical manifestations of infection have a wide spectrum, from the absence of symptoms to diarrhea, malaise, steatorrhea, abdominal cramps, bloating, flatulence, and nausea. Although rare, in some cases proctitis may be clinically relevant.

Direct stool microscopy may reveal trophozoites, especially in liquid feces, while oocysts may be seen in either liquid or solid feces. Limitations of stool microscopy include intermittent excretion of *Giardia* cysts (necessitating up to three stool exams). Antigen detection assays and nucleic acid detection assays have been also developed for detecting *Giardia*. In some cases, duodenal biopsy or aspirate may be required to confirm the diagnosis. First line for treatment of giardiasis is based on metronidazole 400 mg three times daily for 5-10 days. Other effective treatments include tinidazole and nitazoxanide. Alternatives to these medications include paromomycin, mebendazole, albendazole and furazolidone.<sup>76</sup>

## NON INFECTIOUS PROCTITIS

### Radiation therapy

Radiation-associated proctitis is a complication after exposure to x-rays or other ionizing radiation used in the context of radiation therapy for pelvic tumors such as prostate, cervix, uterus, testicles, bladder, rectum, anal or for lymphoproliferative malignancies. Due to its topographic and fixed position in the pelvis, the rectum is highly exposed to damage from radiation therapy. This inflammation can be distinguished in two types, acute or chronic. Acute form, manifesting with the typical proctitis symptoms and endoscopic features, usually occurs within the first 3 months of radiation therapy and is often self-limiting. Chronic proctitis, generally occurs in patients who had suffered from severe acute proctitis, with the median interval of onset ranging between 8 and 13 months.<sup>77</sup> Sometimes it appears as chronic from the beginning, after 3 months of therapy completion. Among the risk factors for its development are included: diabetes mellitus, IBD, smoking, peripheral vascular disease, chemotherapy administration.<sup>78</sup> Typical manifestations are rectal bleeding, tenesmus and symptoms of intestinal obstruction.

Mucosal friability, strictures, fistulas, spontaneous hemorrhage, teleangectasias and ulcerations are distinctive endoscopic features that explain the most reported symptoms. Biopsies, directed at the lateral and posterior walls to avoid the irradiated areas because of the risk of fistula formation, may be helpful in the differential diagnosis and show the presence of eosinophilic crypt abscesses, endothelial arteriole swelling and loss of mucosal cells in the acute form<sup>79,80</sup> whereas arteriolar endarteritis, fibrosis of the lamina propria, crypt distortion, and Paneth cell metaplasia characterize the chronic form.

In absence of large clinical trials, the experiences on treatment are very limited. Three main therapeutic strategies can be considered: medical, endoscopic and surgical. The first line is the

medical therapy which includes: enemas containing drugs with antinflammatory and antioxidant action and beneficial properties for epithelial microvascular injury (5-aminosalicylic acid, sucralfate, short-chain fatty acid, pentoxifylline),<sup>81,82</sup> oral antibiotics (metronidazole), topical applications and oxygen therapy. Endoscopic therapy includes dilation, laser, argon plasma coagulation (APC), cryotherapy, radiofrequency ablation, and mesenchymal stem cell therapy.<sup>83</sup>

In a recent review focused on agents studied for the prevention and treatment of gastrointestinal mucositis (GIM), the evidence continues to support use of probiotics containing *Lactobacillus spp.* for prevention of chemoradiotherapy and radiotherapy-induced diarrhea in patients with pelvic malignancy, and hyperbaric oxygen therapy to treat radiation-induced proctitis. Additional well-designed research is encouraged to enable a decision regarding palifermin, glutamine, sodium butyrate, and dietary interventions, for the prevention or treatment of GIM.<sup>84</sup>

Formaldehyde administration should be attempted before surgical therapy. When surgical therapy is required, a descending or transverse colostomy must be carried out. Advanced methods such as intraperitoneal injections of formalin or novel methods of cold therapy and radiofrequency ablation (RFA) provide a wider remedial field.

Surgical therapy contemplates diversion of the fecal stream via a colostomy or an ileostomy, local repair with reconstruction and mobilization of an advanced flap in cases of fistulas and, for more severe or refractory cases, proctectomy.<sup>85,86</sup>

Since aggressive treatments like coloanal anastomosis and colorectal surgery are correlated with remarkable mortality and morbidity, they must be considered as the final course of remedial treatment.

Radiation injury can be limited through two main strategies: reducing the dose delivered to adjacent structures using, for example, intensity-modulated, volumetric-modulated and 3-dimensional conformal radiation therapy<sup>87</sup> or brachytherapy; reducing the radiosensitivity of the organs at risk, using some medications such as amifostine, a prodrug that scavenges oxygen free radicals, used intravenously in some randomized trials.<sup>88</sup>

## Surgical diversion

First described as a new entity in 1981 by Glotzer et al.,<sup>88</sup> diversion proctitis is an inflammatory disease involving the excluded rectum, which is diverted from the fecal stream by surgical interventions, and is part of the broader spectrum defined as radiation colitis. Its incidence as well as its pathogenesis are still unknown. Different pathogenetic mechanisms have been proposed but data

supporting them are very limited. Among the hypothesized models are included: bacterial overgrowth, presence of harmful bacteria, toxins or disturbance in the symbiotic relationship between luminal bacteria and the mucosal layer and nutritional deficiency.<sup>90</sup> Usually, the onset is between 3 and 36 months after fecal diversion.

Endoscopic features are various: erythema, mucous plugs, granularity, friability, blurring of vascular pattern, aphthous ulcers, spontaneous bleeding, nodularity, edema, inflammatory polyps, and strictures. No pathognomonic signs have been identified up to now and biopsies can reveal lymphoid follicular hyperplasia, which is one of the commonest finding, crypt distortion, regenerative hyperplasia, Paneth cell metaplasia, thickening of muscularis mucosa, diffuse active mucosal inflammation with crypt abscess, ulceration, vacuolar and epithelial degeneration. In most cases, inflammatory changes and symptoms related are resolved after re-establishment of gastrointestinal continuity.<sup>90</sup>

## Ischemic damage

Ischemic involvement of the rectum takes place in 5% of the cases of ischemic colitis. Indeed, in 75% damage is located in colon and, frequently, in the splenic flexure, because the rectum has a wide arterial supply network from the inferior mesenteric, internal iliac, internal pudendal arteries and the marginal artery.<sup>92</sup> Elderly patients with significant atherosclerotic disease compromising blood flow and cardiac risk factors are the subjects most frequently exposed to developing ischemic proctitis.<sup>93</sup> Conditions at risk include those implying the possibility to develop a sudden acute compromise in blood flow: previous vascular intervention, aorto-iliac surgery, radiotherapy and hypotensive shock.<sup>94</sup> Spontaneous ischemic proctitis is a very rare event, limited to less than 2% of all cases of ischemic colitis. Severity can be various: in transient ischemia damages are generally reversible and limited to the superficial mucosal layers, consisting of edema and hemorrhage, but, in prolonged ischemia, mucosal necrosis with ulceration and/or perforation may lead to fatal consequences.

Clinical presentation is not different from the other etiologies and is often misleading. In support to the diagnosis computed tomography (CT) scan can give a contribution of suspicion, but colonoscopy, performed within 48 h from the beginning of the symptoms, remains the more reliable tool, allowing, also, to do biopsies which are generally useful in confirming diagnosis.<sup>95</sup>

In the early stages of treatment, the most important aspect is monitoring vital parameters and restoration of the patient's blood volume in order to maintain or improve the cardiac output. When ischemia is transient this management is generally enough to induce recovery and avoid worsening. Careful clinical observation is of paramount importance to catch early signs of sepsis or perforation.



Broad-spectrum antibiotics can be necessary in this context. The most severe cases, inducing perforation, may require surgical interventions: abdominal perineal resection or, when the lower rectum is spared, a low anterior resection, represents the commonest adopted technique.<sup>96</sup>

## Traumatisms

Chronic traumatism linked to prolonged and repetitive practice of masturbation with anal objects can lead to the appearance of ano-rectal lesions similar to those described for other forms of proctitis. In addition to the essential anamnestic information, some features help to depose mainly for a traumatic form: tears, abrasions, hematoma, discoloration with tenderness, fissures. Similar speech can be made for injuries observed after anal intercourse, fisting, which could also cause rectal perforation or a lesion of anal sphincters, and sexual abuse.<sup>97</sup>

## Conclusions

Nowadays, it is increasingly more common in a gastroenterological setting, to come across of cases of proctitis whose nature is not ascribable to IBD. The clinical and endoscopic characteristics, on their own, configure clinical pictures that are difficult to distinguish from one another. When it is necessary to exclude all other forms of proctitis for which the anamnestic data plays a fundamental role, specifically referring to radiation, diversion, ischemic and traumatic form, the clinician is faced with the great chapter of the proctitis of infectious origin. As a matter of fact, in the last years, it has been registered a growing incidence of infectious proctitides, particularly in MSM, within the broader context of STIs. Although the clinical presentation may be undistinguishable from an ulcerative colitis or a Crohn's disease involving ano-rectal region, the response to standard treatments adopted for IBD is inadequate. In order to avoid this kind of mistakes, clinicians are required to proceed in a reasoned manner, that is to say starting with the collection of an in-depth medical history aimed at assessing life-style, recent traveling and sexual habits, including anal intercourse. In addition, it is essential to perform a focused physical examination which can help to highlight salient traits attributable to a particular etiology. Based on these findings, it is possible to start an empirical treatment with antibiotics or antivirals. Further diagnostic tools may contribute to the diagnosis such as culture, PCR, serology and endoscopy. Once an infectious cause has been identified it should be provided information to patients about transmission risks to partners and it should be emphasized the importance that also partners undergo to investigations, due to the high risk of contagion. It is advisable for gastroenterologists to refer to an expert in sexual health and associated infections, in order to improve the management of these patients. As very frequent, co-infection with other sexually

transmitted pathogens should be investigated and a complete screening including HIV, first of all, but also hepatitis B (HBV) and hepatitis C (HCV)<sup>98</sup> viruses should be taken into consideration. With a timely and appropriate treatment, the long-term prognosis of infectious proctitis is auspicious.

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